SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF DRUG PRODUCT

Advantec Tablets 16mg + 12.5mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains:
Candesartan Cilexetil…… 16mg
Hydrochlorothiazide USP……. 12.5mg

3. PHARMACEUTICAL FORM

Peach colored square shaped tablet, marked bisect line on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ADVANTEC (Candesartan Cilexetil + Hydrochlorothiazide) is indicated for the treatment of hypertension. The fixed dose combination is not indicated for initial therapy.

4.2 Posology and Method of Administration

The usual starting dose of ADVANTEC (Candesartan Cilexetil + Hydrochlorothiazide) is one tablet per day with or without food. To minimize dose dependent side effects, it is usually appropriate to begin combination therapy only after a patient has failed to achieve the desired effect with monotherapy.

Dose Titration
A patient whose blood pressure is not controlled on 25mg of hydrochlorothiazide once daily can expect an incremental effect from ADVANTEC (Candesartan Cilexetil + Hydrochlorothiazide). A patient whose blood pressure is controlled on 25mg of hydrochlorothiazide but is experiencing decreases in serum potassium can expect the same or incremental blood pressure effects from ADVANTEC (Candesartan Cilexetil + Hydrochlorothiazide) and serum potassium may improve.

Renal Impaired Patients:
The usual regimens of therapy with ADVANTEC (Candesartan Cilexetil + Hydrochlorothiazide) may be followed as long as the patient's creatinine clearance is > 30mL/min.

Hepatic Impaired Patients:
The usual regimens of therapy with ADVANTEC (Candesartan Cilexetil + Hydrochlorothiazide) may be followed in patients with mild hepatic impairment. In patients with moderate hepatic impairment, consideration should be given to initiation of ADVANT (Candesartan Cilexetil) at a lower dose, such as 8mg. If a lower starting dose is selected for

candesartan cilexetil, ADVANTEC (Candesartan Cilexetil + Hydrochlorothiazide) is not recommended for initial titration because the appropriate initial starting dose of candesartan Cilexetil cannot be given.

4.3 Contraindications:

ADVANTEC (Candesartan Cilexetil + Hydrochlorothiazide) is contraindicated:

- In patients who are hypersensitive to this drug or any component of this product.
- In patients with anuria or hypersensitivity to other sulfonamide-derived drugs, due to hydrochlorothiazide component in the preparation.
- In concomitant use with other antihypertensive drugs like, dofetilide.
- In patients with more severe renal impairment.

4.4 Special warnings and special precautions for use

USE IN PREGNANCY

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, ADVANTEC should be discontinued as soon as possible.

Hypotension in Volume- and Salt-Depleted Patients

In patients with an activated renin-angiotensin system, such as volume and/or salt-depleted patients (e.g., those being treated with diuretics), symptomatic hypotension may occur. These conditions should be corrected prior to administration of ADVANTEC, or the treatment should start under close medical supervision.

Candesartan Cilexetil:

Impaired Renal Function

As a consequence of inhibiting the renin angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals treated with candesartan.

In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen (BUN) have been reported. There has been no long-term use of candesartan in patients with unilateral or bilateral renal artery stenosis, but similar results may be expected.

Hydrochlorothiazide:

- *Impaired Hepatic Function*

  Thiazide diuretics should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma.

- *Impaired Renal Function*

  Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

- *Hypersensitivity Reaction*

Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history.

- Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.
- Periodic determination of serum electrolytes to detect possible electrolyte
- imbalance should be performed at appropriate intervals.
- Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function.

4.5 Interaction with other medicaments

Candesartan Cilexetil

Lithium
An increase in serum lithium concentration has been reported during concomitant administration of lithium with candesartan cilexetil, so careful monitoring of serum lithium levels is recommended during concomitant use.

Hydrochlorothiazide

When administered concurrently the following drugs may interact with thiazide Diuretics.

Alcohol, barbiturates or narcotics
Potentiation of orthostatic hypotension may occur.

Anti-diabetic (Oral agents and insulin)
Dose adjustment for anti-diabetic drug may be required.

Chloestyramine and colestipol resins
Single dose of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from gastrointestinal tract by up to 85% and 43% respectively.

Corticosteroids, ACTH
Intensified electrolyte depletion, particularly hypokalemia.

Pressor amines (norepinephrine)
Possible decreased response to pressor amines but not sufficient to preclude their use.

Skeletal muscle relaxant (tubocurarine)
Possible increased responsiveness to the muscle relaxant.

Lithium
Hydrochlorothiazide reduces the renal clearance of lithium and a high risk of lithium toxicity.

NSAIDs
When ADVANTEC and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

4.6 Fertility, pregnancy and lactation

Pregnancy

When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, ADVANTEC should be discontinued as soon as possible.

Nursing Mothers

Hydrochlorothiazide is excreted in breast milk but it is not known whether candesartan is excreted in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

4.7 Effects on ability to drive and operate machines

Candesartan Cilexetil + Hydrochlorothiazide unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur during treatment of hypertension.

4.8 Undesirable effects

Adverse reactions reported with candesartan cilexetil + hydrochlorothiazide are mild and transient in nature and have only infrequently required discontinuation of therapy.

Common
Back pain, dizziness, flu-like symptoms, headache, upper respiratory infection.

Less Common
Abdominal pain, change in amount of urine, increased sweating, unusual thirst, fainting, gastrointestinal disorders, mood swings.

Rare
Persistent sore throat, cough, fever, unusual fatigue, unusual bleeding or bruising, pale skin and eyes, dark urine, chest pain, irregular heartbeats, joint pain.

4.9 Overdosage

Based on pharmacological considerations, the main manifestation of an overdose Candesartan Cilexetil is likely to be symptomatic hypotension and dizziness. In individual case reports of overdose (of up to 672 mg Candesartan Cilexetil) patient recovery was uneventful. The main manifestation of an overdose of hydrochlorothiazide is acute loss of fluid and electrolytes. Symptoms such as dizziness, hypotension, thirst, tachycardia, ventricular arrhythmias, sedation/impairment of consciousness and muscle cramps can also be observed.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic Group: Angiotensin II Receptor Antagonist (ARB)

ATC Code: C09DA06

5.1 Pharmacodynamic properties

Mechanism of Action:

Candesartan Cilexetil:
Candesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is, therefore, independent of the pathways for angiotensin II synthesis.
Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because candesartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Candesartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Hydrochlorothiazide:
Hydrochlorothiazide is a thiazide diuretic. Thiazides affect the renal tubular mechanisms of electrolyte reabsorption, directly increasing excretion of sodium and chloride in approximately equivalent amounts. Indirectly, the diuretic action of hydrochlorothiazide reduces plasma volume, with consequent increases in plasma renin activity, increases in aldosterone secretion, increases in urinary potassium loss, and decreases in serum potassium. The renin-aldosterone link is mediated by angiotensin II, so co-administration of an angiotensin II receptor antagonist tends to reverse the potassium loss associated with these diuretics. The mechanism of the antihypertensive effect of thiazides is unknown.

5.2 Pharmacokinetic Properties

Absorption:

Candesartan Cilexetil
Following oral administration of candesartan cilexetil, the absolute bioavailability of candesartan was estimated to be 15%. After tablet ingestion, the peak serum concentration (Cmax) is reached after 3 to 4 hours. Food with a high fat content does not affect the bioavailability of candesartan after candesartan cilexetil administration.

Hydrochlorothiazide
Hydrochlorothiazide is incompletely but fairly rapidly absorbed from the gastrointestinal tract. Peak plasma concentrations occur between 60 and 120 minutes. Absorption is enhanced when given with food.

Distribution:

Candesartan Cilexetil
After single and repeated administration, the pharmacokinetics of candesartan is linear for oral doses up to 32mg of candesartan cilexetil. Candesartan and its inactive metabolite do not accumulate in serum upon repeated once-daily dosing.

The volume of distribution of candesartan is 0.13L/kg. Candesartan is highly bound to plasma proteins (>99%) and does not penetrate red blood cells. The protein binding is constant at candesartan plasma concentrations well above the range achieved with recommended doses.

Hydrochlorothiazide
Hydrochlorothiazide preferentially binds to red blood cells. It crosses placental barrier and distributes into breast milk.

Metabolism:

Candesartan Cilexetil
Candesartan cilexetil is rapidly and completely bioactivated by ester hydrolysis during absorption from the gastrointestinal tract to candesartan, a selective AT1 subtype angiotensin II receptor antagonist.
Candesartan undergoes minor hepatic metabolism by O-deethylation to an inactive metabolite.

Hydrochlorothiazide
Hydrochlorothiazide is not metabolized but is eliminated rapidly by the kidney.

Excretion:

Candesartan Cilexetil
When candesartan is administered orally about 26% of the dose is excreted unchanged in urine. Total plasma clearance of candesartan is 0.37mL/min/kg, with a renal clearance of 0.19mL/min/kg. The elimination half-life of candesartan is approximately 9 hours.

Hydrochlorothiazide
Hydrochlorothiazide is excreted unchanged into urine, 50% being recovered within the first 12 hours and 70% by 4 days. 11 – 25% of an oral dose may appear in the faeces. The terminal half-life of hydrochlorothiazide is 5-15 hours.

Special Populations:

Pediatric
The pharmacokinetics of Candesartan Cilexetil have not been investigated in patients <18 years of age.

Geriatric

The plasma concentration of candesartan was higher in the elderly (Cmax was approximately 50% higher, and AUC was approximately 80% higher) compared to younger subjects administered with the same dose. No initial dosage adjustment is necessary.

Renal Insufficiency

In hypertensive patients with renal insufficiency, serum concentrations of candesartan were elevated. After repeated dosing, the AUC and Cmax were approximately doubled in patients with severe renal impairment (creatinine clearance <30mL/min/1.73m2) compared to patients with normal kidney. No initial dosage adjustment is necessary in patients with mild renal

insufficiency. In patients with impaired renal function (mean creatinine clearance of 19mL/min), the half-life of hydrochlorothiazide elimination was lengthened to 21 hours.

Hepatic Insufficiency
The increase in AUC for candesartan was 30% in patients with mild hepatic impairment (Child-Pugh A) and 145% in patients with moderate hepatic impairment (Child-Pugh B). The increase in Cmax for candesartan was 56% in patients with mild hepatic impairment and 73% in patients with moderate hepatic impairment. The pharmacokinetics after candesartan cilexetil administration have not been investigated in patients with severe hepatic impairment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

- Lactose Monohydrate
- Pharmacoat 606 (HPMC)
- Sodium Lauryl Sulfate
- Carboxy Methyl Cellulose Calcium
- Ferric Oxide Red
- Magnesium Stearate

6.2 Incompatibilities

Not applicable

6.3 Shelf-life

3 Years

6.4 Special precautions for storage

- Store below 30°C.
- Protect from sunlight & moisture.
- The expiration dates refer to the product correctly stored in the required conditions.

6.5 Nature and contents of container

ADVANTEC (Candesartan Cilexetil + Hydrochlorothiazide) 16mg + 12.5mg tablets are available in Alu-Alu blister packs of 28’s.

6.6 Special precautions for disposal

No special requirements.

6.7 Instructions for use/handling

- Keep out of reach of children.
- To be sold on prescription of a registered medical practitioner only.

7. MARKETING AUTHORISATION HOLDER

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8. PRODUCT REGISTRATION NUMBER

039428
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9. DATE OF PRODUCT REGISTRATION ISSUED

12 July 2005
07 Sept 2018